Lisocabtagene maraleucel (Breyanzi®) for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B)

General information [1]

Drug description	Indication
Lisocabtagene maraleucel (Breyanzi®) is a CD19-directed genetically modified autologous cellular immunotherapy, where the chimeric antigen receptor (CAR) binds to CD19 expressed on the cell surface of tumour and normal B cells. This induces activation and proliferation of CAR T cells, release of pro-inflammatory cytokines, and cytotoxic killing of target cells.	Lisocabtagene maraleucel (Breyanzi®) is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), after two or more lines of systemic therapy.

Current treatment [2]

- Patients with relapsed/refractory DLBCL who are eligible for transplant should receive intensive salvage regimens with rituximab and chemotherapy followed by (in responsive patients) autologous or allogeneic stem cell transplantation (ASCT).
- Salvage regimens such as R-DHAP or R-ICE appear to have similar outcomes.
- The main goal of salvage is to reduce disease burden and demonstrate continued chemotherapy sensitivity prior to ASCT, but salvage chemotherapy is also beneficial even if not followed by transplantation.
- NICE also recommends considering R-GDP immunochemotherapy, which is as effective as other commonly used salvage regimens and less toxic.
- Pixantrone monotherapy is recommended as an option for treating patients with multiple relapsed or refractory aggressive DLBCL only if the patient has previously been treated with rituximab and the patient is receiving third- or fourth-line treatment and the manufacturer provides pixantrone with the discount agreed in the patient access scheme.
- Patients not suitable for high-dose therapy may be treated with the same or other salvage regimens as R-GEMOX.

Regulatory status

EMA

Approval status for this indication: On 27 January 2022, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Breyanzi®. As Breyanzi® is an advanced therapy medicinal product, the CHMP positive opinion is based on an assessment by the Committee for Advanced Therapies.

UPDATE: Date of issue of marketing authorisation valid throughout the European Union: 04/04/2022

The full indication is:

- Breyanzi® is indicated for the treatment of adult patients with relapsed or refractory DLBCL, PMBCL and FL3B, after two or more lines of systemic therapy.

Breyanzi® will be available as 1.1-70 × 106 cells/mL (CD_4+ cells) / 1.1-70 × 106 cells/mL (CD8+ cells) dispersion for infusion.

Breyanzi® contains the following two active substances, which are covered by the single INN lisocabtagene maraleucel:

- CD19-directed genetically modified autologous cell-based product consisting of purified CD8+ T cells (CD8+ cells)
- CD19-directed genetically modified autologous cell-based product consisting of purified CD_4+ T cells (CD_4+ cells).

Other indications: none

FDA [4]

Approval status for this indication: On 5 February 2021, the FDA approved Breyanzi® to treat adult patients with certain types of large B-cell lymphoma who have not responded to, or who have relapsed after, at least two other types of systemic treatment.

Breyanzi® is the third gene therapy approved by the FDA for certain types of non-Hodgkin lymphoma, including diffuse large B-cell lymphoma (DLBCL). Breyanzi® is not indicated for the treatment of patients with primary central nervous system lymphoma.

- ✓ Orphan Drug designation
- ✓ Regenerative Medicine Advanced Therapy (RMAT) designation
- ✓ Breakthrough Therapy designations

Other indications: none

✓	**Additional monitoring**	

Costs

Currently, no cost information is available.

Warnings and precautions [5]

- **Cytokine release syndrome (CRS)**
  - CRS, including fatal or life-threatening reactions, occurred in patients receiving Breyanzi®.
  - Do not administer Breyanzi® to patients with active infection or inflammatory disorders.
  - Treat severe or life-threatening CRS with tocilizumab with or without corticosteroids.
- **Neurologic toxicities**
  - Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving Breyanzi®, including concurrently with CRS, after CRS resolution, or in the absence of CRS.
  - Monitor for neurologic events after treatment with Breyanzi®.
  - Provide supportive care and/or corticosteroids as needed.
- **Hypersensitivity reactions**
  - Monitor for hypersensitivity reactions during infusion.
- **Serious infections**
  - Monitor patients for signs and symptoms of infection; treat appropriately.
- **Prolonged cytopenias**
  - Patients may exhibit Grade 3 or higher cytopenias for several weeks following Breyanzi® infusion.
  - Monitor complete blood counts.
- **Hypogammaglobulinemia**
  - Monitor and consider immunoglobulin replacement therapy.
- **Secondary malignancies**
  - Patients treated with Breyanzi® may develop secondary malignancies. Monitor lifelong for secondary malignancies.
- **Effects on ability to drive and use machines**
  - Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery for at least 8 weeks after Breyanzi® administration.

Study characteristics [6-8]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
TRANSCEND NHL 001 NCT02631044	269	Lisocabtagene maraleucel as two sequential infusions of CD8+ and CD4+ CAR+ T cells, at one of three target dose levels: 50×10^6 CAR+ T cells (dose level 1, n=45) or 50×10^6 CAR+ T cells in two doses (dose level 1D, n=6), 100×10^6 CAR+ T cells (dose level 2, n=166), and	-	AEs, dose-limiting toxicities, and the	**Ongoing**[2], multicentre, multicohort, seamless design study	-	Juno Therapeutics, a Bristol-Myers Squibb Company	[7]

[2] Estimated study completion date is 12/2022.

		150 × 10^6 CAR+ T cells (dose level 3, n=41)		ORR (assessed by Lugano criteria)[1]				

Efficacy	Safety (n=269)
Dose-limiting toxicities (n=139 evaluable) ❖ **Dose-limiting toxicities**: 6.0% (including one patient who died of diffuse alveolar damage at dose level 1) ❖ **No** maximum-tolerated dose was identified. ❖ An increased rate of grade 1–2 cytokine release syndrome at dose level 3 and a numerically higher ORR at dose level 2 and dose level 3 supported the selection of dose level 2 (**100 × 10^6 CAR+ T cells**) for the dose-confirmation phase. **Efficacy-evaluable set (n=256)** **Objective response**: 73.0%, 95% CI 66.8–78.0; one-sided p<0.0001 **Complete response**: 53.0%, 46.8–59.4; one-sided p<0.0001 16 patients who achieved a complete response after lisocabtagene maraleucel treatment but later progressed received retreatment with lisocabtagene maraleucel. **Median time to first complete response or partial response**: 1.0 months (range 0.7–8.9) **Time to first complete response**: 1.0 months (0.8–12.5) **Median duration of response**: not reached (95% CI 8.6–not reached) at median follow-up for duration of response of 12.0 months (95% CI 11.2–16.7). **Estimated duration of response rate at 1 year**: 55.0% (95% CI 46.7–62.0) for the total population, 65.0% (56.2–72.8) among those who achieved a complete response. **Median PFS**: 6.8 months (95% CI 3.3–14.1) after median follow-up for PFS of 12.3 months (95% CI 12.0–17.5) **Median PFS among patients who achieved a complete response**: not reached **PFS at 1 year**: 44.0% (95% CI 37.3–50.7) for the total population and 65.0% (56.1–72.7) among patients who had complete response. **Median OS:** 21.1 months (95% CI 13.3–not reached), with median follow-up for OS of 17.5 months (95% CI 12.9–17.8). **Estimated 12-month OS**: 58.0% (95% CI 51.3–63.8) for the total population **Median OS among patients who achieved a complete response**: not reached; OS: 86.0% (95% CI 78.2–90.5) at 1 year. **Activity of lisocabtagene maraleucel**: similar across dose levels, with no difference noted between individual dose levels for ORR (p=0.68), PFS (p=0.46), or duration of response (p=0.76), or between analysis sets.	**Treatment-emergent AEs of grade ≥3:** n=213/269 (79.0%) **Deaths due to treatment-emergent AEs**: n=7/269 (3.0%)[3] **Cytokine release syndrome of any grade:** n=113/269 (42.0%) **Cytokine release syndrome grade ≤3:** n=6/269 (2.0%) **Neurological events of any grade:** n=80/269 (30.0%) **Neurological events of grade ≥3:** n=27/269 (10.0%)

[1] Endpoints were assessed by an independent review committee in the efficacy-evaluable set (comprising all patients who had confirmed PET-positive disease and received at least one dose of lisocabtagene maraleucel).

[3] Causes were (n=1 for each) diffuse alveolar damage (dose-limiting toxicity), pulmonary haemorrhage, multiple organ dysfunction syndrome, cardiomyopathy, leukoencephalopathy, septic shock, and progressive multifocal leukoencephalopathy. Diffuse alveolar damage, pulmonary haemorrhage, multiple organ dysfunction syndrome, and cardiomyopathy were considered related to both lisocabtagene maraleucel and lymphodepleting chemotherapy by the investigator.

Primary analysis set (which comprised patients in the efficacy-evaluable set who received dose level 2**)** Objective response: 74.0%, 95% CI 66.2-81.6; one-sided p<0.0001 Complete response: 54.0%, 95% CI 45.3–62.8; one-sided p<0.0001 **Intention-to-treat set** (n=344 patients who underwent leukapheresis) Objective response: 61.0%, 95% CI 55.1–65.7 patients; one-sided p<0.0001 Complete response: 44.0%, 95% CI 38.3–49.0; one-sided p<0.0001 **Patients evaluable for cellular kinetic analyses (n=245)** Median time to CAR T-cell peak expansion across all dose levels: 12 days (IQR 10–14) Median maximum expansion (C_{max}) was 23 928.2 copies per µg Median area under the curve from 0–28 days post-infusion (AUC0–28d): 213 730.1 day × copies per µg CAR T cells showed long-term persistence at 1 year in 52% of patients. **UPDATE**: Efficacy set (n=216) results (median on-study follow-up time of 19.9 months) [9]: Overall response rate: 72.2%, 95% CI 66.2-78.5 Complete response: 53.2%, 95% CI 46.4-60.0 Partial response: 19.4%, 95% CI 14.4-25.4 Median duration of response: 20.2 months, 95% CI 8.2-not reached Median duration of response if best response is complete response: 26.1 months, 95% CI 23.1-not reached	

Risk of bias - study level (case series) [10]

1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	yes	yes	yes	yes	yes	yes	no
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	yes	yes	yes	unclear	yes	yes	unclear	yes
Overall risk of bias: moderate								

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Abbreviations: AE=adverse event, AJ=adjustment, ASCT=allogeneic stem cell transplantation, C=comparator, CAR=chimeric antigen receptor, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CRS=Cytokine release syndrome, DLBCL=diffuse large B cell lymphoma, EMA =European Medicines Agency, FDA=Food and Drug Administration, FL3B=follicular lymphoma grade, HR=hazard ratio, I=intervention, Int.=intention, MG=median gain, n=number of patients, NICE=National Institute for Health and Care Excellence, OS=overall survival, ORR=Objective response rate, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade,

PMBCL=primary mediastinal large B-cell lymphoma, QoL=quality of life, R-DHAP=Rituximab + Dexamethasone + Cytarabine + Cisplatin, R-GDP=rituximab+gemcitabine+dexamethasone+cisplatin, R-GEMOX=rituximab+gemcitabine+oxaliplatin, R-ICE=rituximab+ifosfamide+carboplatin+etoposide phosphate, SAE=serious adverse event, ST=standard treatment

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